and

wherein the detecting of said low-molecular weight peptides is effected by parameters such as molecular weight;

relating substantially of the detected said low-molecular weight peptides to a reference; and

said reference comprises a distribution of low-molecular weight peptides in a representative cross-section of defined controls to produce a differential peptide display.

REMARKS

Reconsideration of this patent application is respectfully requested in view of the foregoing amendments and the following remarks.

As requested by the Patent Examiner, enclosed is a Marked-Up Copy of Specification pages 1, 2, 8 and 16 showing numbers in the margin.

The amendments to the Specification are to add the phrase "What Is Claimed" to the Claims page. Amendments of present Claim 1 concern the introduction of "substantially the entirety

of" between the wording "measuring" and "peptides from a set sample..." in line 11 of claim 1; furthermore the introduction of the wording "substantially of the detected" between "relating" and "said low molecular weight peptides..." in line 5 from the bottom of Claim 1.

The claim amendments were introduced in order to distinguish the claimed process over the prior art applied by the Patent Examiner. *Jimenez* does not use the entirety of the peptides found, but specific ones. In FIG. 2 on page 4 or 6 of the *Jimenez* reference, some of the peptides are not considered. *Jimenez* uses only known and sequenced peptides, however, and does not rely on the analysis of all the peptides found in sample. Also *Harry* and *Ausubel* each has measured specific antigens such as for detecting HIV in *Harry*. *Harry* also did not measure all the peptides, which are present in the sample. *Ausubel* does not measure all the peptides in the sample.

Of course, a person skilled in the art does not have any incentive to modify the teachings of *Harry* and/or *Jimenez* and/or *Ausubel* in such way that the entirety of the peptides in the sample (low molecular peptides) should be measured. The skilled

person does not have any reasonable expectation of success concerning the very different method steps according to the present invention.

Also enclosed is a self-explanatory Declaration of Dr. Schulz-Knappe PhD, which answers the various formal objections of the Patent Examiner under 35 U.S.C. 112. Withdrawal of this ground of rejection is respectfully requested.

Based upon the enclosed Declaration by Dr. Peter Schulz-Knappe, the prior art rejections under 35 U.S.C. 102 over *Harry*, *Ausubel* and *Jimenez* are believed to be overcome.

Also, none of the prior art references discloses the detection of qualitative and quantitative changes. This is an important improvement and advantage of the present invention, as discussed in the paragraph bridging pages 7 and 8 of the present Specification, as follows.

The data about patients with a known basic disease obtained from the above mentioned steps are compared to the similarly obtained data from a healthy reference population. Both

qualitative changes (e.g., the occurrence of new peptides or the lacking of peptides) and quantitative changes (the increased or decreased occurrence of individual peptides) are detected. If required, the targets defined by the comparative analysis may further be purified and identified by methods of peptide chemistry known to those skilled in the art. The sequence information obtained can then be compared with protein and nucleic acid data bases and subsequently with data from the literature. The relevance of the represented peptides with respect to the examined disease is checked by functional studies and by screening with appropriate groups of patients.

For all of the above reasons, none of the prior art references provides an identical disclosure of the claimed invention. Hence, the present invention is not anticipated under 35 U.S.C. 102. Withdrawal of this ground of rejection is respectfully requested.

Also, none of the prior art references teaches or suggests the present invention as claimed and none of the prior art references provides a basis for any rejection of the claims under 35 U.S.C. 103. A prompt notification of allowability is

respectfully requested.

Respectfully submitted,
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Enclosures: (1) Copy of Petition for Three Month Extension of Time for a Small Entity;
(2) Marked Up Copy Amended Claim and Specification;
(3) Declaration of Dr. Peter Schulz-Knappe;
(4) Check for $460.00.

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to: Assistant Commissioner of Patents, Washington, D.C. 20231, on October 24, 2001.

Lisa L. Vulpis

MARKED-UP VERSION
OF
AMENDED CLAIM
AND
AMENDED SPECIFICATION

1. (Three Times Amended). A method for detecting a pathogenic or any other condition of an organism comprising the steps of

taking a sample, and said sample is selected from the group consisting of a tissue sample, a fluid sample from said organism, the organism itself, the combinations thereof; and

wherein said organism is selected from the group consisting of a procarvote, a eucarvote, a multicellular organism, cells from tissue cultures, and cells from animals and humans;

measuring substantially the entirety of peptides from said sample of said organism containing high-molecular weight peptides and low-molecular weight peptides, as an indication of the pathogenic or any other condition of said organism;

wherein said low-molecular weight peptides, used for said measurement have a molecular weight of not more than 30,000 Dalton;

directly detecting said low molecular weight peptides; and

wherein the detecting of said low-molecular weight peptides is effected by parameters such as molecular weight;

relating substantially of the detected said low-

molecular weight peptides to a reference; and

said reference comprises a distribution of low-molecular weight peptides in a representative cross-section of defined controls to produce a differential peptide display.

SMB

A method for detecting the condition of an organism through the measurement of peptides

1. Field of the Invention

The present invention relates to a method for detecting the condition of an organism through the measurement of peptides from a sample of said organism.

2. The Prior Art

Various analytical methods are employed for detecting the condition of an organism. Thus, for example, in the diagnostics of higher organisms, when pathological results are obtained, attempts are made to fathom the causes of the pathological change on the basis of the symptoms in order to develop a causal therapy. Further, efforts are being made to develop a reference of an average "healthy" organism by sequencing the genomes of organisms and establishing "wild type genomes" in order to be able to discover individual deviations which could indicate possible pathogenic developments by performing corresponding gene analyses. A drawback of the first methodological approach is that diagnostics free from hypotheses (bias-free) cannot be performed since the diagnostics therein are already based on assumptions. A drawback of the second method is that it will not be possible for a long time to diagnose the important or even all diseases attributed to genetic dysfunctions. Another drawback of the latter method may also be that a mutation on a gene does not necessarily result in expression of the related phenotype.

Thus, it would be desirable to provide a universally employable diagnostic method by which it is possible to avoid the drawbacks mentioned and, in particular, to perform diagnostics free

from hypotheses. In addition, the diagnostic method should be universally employable, not be restricted to higher developed systems, but also be employable for detecting the condition of lower organisms. In addition, it should be easy to establish and capable of being carried out with per se known techniques.

SUMMARY OF THE INVENTION

Thus, it has been the object of the present invention to provide such a method.

Surprisingly, the object of the invention is achieved in a simple manner by a method with the features of claim 1. The subclaims pertain to preferred embodiments of the method according to the invention.

The method according to the invention for detecting the condition of an organism starts by taking a sample from the organism to be examined. This sample may also be the complete organism. The sample must contain low-molecular weight peptides, but there is no interference from high-molecular weight peptides or proteins which are also contained in the sample in addition to low-molecular weight peptides. According to the invention, the low-molecular weight peptides are directly detected and characterized and serve as indicators of the condition of the organism. It is possible to detect single peptides directly by a measuring technique, to detect several peptides by a measuring technique, or even all the low-molecular weight peptides present in the sample which can be detected by a measuring technique. Unlike conventional analytical or diagnostic methods, such as gel electrophoresis or two-dimensional electrophoresis and, for example, clinical diagnostic methods, the method according to the invention does not examine the high-molecular weight structures, such as proteins. As opposed to per se known diagnostic methods, such as radioimmunoassay or other competitive assays for the measurement of peptide hormones and the like, the low-molecular weight peptides are directly detected according to the invention by some measuring technique rather

istry known to those skilled in the art. The sequence information obtained can then be compared with protein and nucleic acid data bases and subsequently with data from the literature. The relevance of the represented peptides with respect to the examined disease is checked by functional studies and by screenings with appropriate groups of patients.

DETAILED DESCRIPTION PART EMBODIMENTS

Example 1

Use of body fluids: blood filtrate (hemofiltrate, HF)

1. Recovery of HF

HF is recovered by arterio-venous or veno-venous hemofiltration performed by techniques known to those skilled in the art with selected patients or subjects. The recovery of HF is effected in the same way, in principle, as performed as a matter of routine in patients with chronical renal disease. Through an arterial drain and venous feed (arterio-venous hemofiltration) or venous drain and venous feed (veno-venous hemofiltration), the patient's blood is passed with the aid of a hemofiltration device (e.g., Hemoprozessor, Sartorius, Göttingen; AK 10 HFM, Gambro, Hechingen) through a hemofilter (e.g., Hemoflow F 60 or Hemoflow HF 80 S, Fresenius, Bad Homburg; Hemoflow FH 77 H and Hemoflow HF 88 H, Gambro) which has a molecular exclusion size of up to 30 kDa. The filtrate volume withdrawn from the patient is substituted by an electrolyte solution (e.g., SH 01, SH 05, SH 22, SH 29, Schiwa, Glandorf).

According to the present method, a diagnostic hemofiltration is performed with the aim to obtain from 1 to 30 l of HF from a patient in the course of one hemofiltration. For avoiding proteolysis, the hemofiltrate is immediately adjusted to a pH value between 2 and 4 with diluted acid (e.g., 1 M HCl), and cooled to 4 °C.

C L A I M S :

WHAT IS CLAIMED:

1. A method for detecting the condition of an organism through the measurement of peptides from a sample of said organism containing high- and low-molecular weight peptides, as an indication of the condition of said organism, wherein

   - low-molecular weight peptides are directly detected and characterized; and

   - related to a reference.

2. The method according to claim 1, wherein said sample is tissue or fluid samples from said organism, or the organism itself, or combinations thereof.

3. The method according to claims 1 and/or 2, wherein said low-molecular weight peptides used for said measurement have a molecular weight of not more than 30,000 Dalton.

4. The method according to claim 3, wherein said low-molecular weight peptides used for said measurement have a molecular weight which at least corresponds to that of dipeptides.

5. The method according to claims 3 and/or 4, wherein said low-molecular weight peptides used for said measurement have a molecular weight of from 100 to 10,000 Dalton.

6. The method according to at least one of claims 1 to 5, wherein said high-molecular weight peptides are separated off prior to measurement of said low-molecular weight pep-